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Amifostine Analogue, Drde-30, Attenuates Radiation-Induced Lung Injury in Mice

Authors : Aastha Arora, Vikas Bhuria, Saurabh Singh, Uma Pathak, Shweta Mathur, Puja P. Hazari, Rajat Sandhir, Ravi Soni, Anant N. Bhatt, Bilikere S. Dwarakanath

Abstract : Radiotherapy is an effective curative and palliative option for patients with thoracic malignancies. However, lung injury, comprising of pneumonitis and fibrosis, remains a significant clin¬ical complication of thoracic radiation, thus making it a dose-limiting factor. Also, injury to the lung is often reported as part of multi-organ failure in victims of accidental radiation exposures. Radiation induced inflammatory response in the lung, characterized by leukocyte infiltration and vascular changes, is an important contributing factor for the injury. Therefore, countermeasure agents to attenuate radiation induced inflammatory response are considered as an important approach to prevent chronic lung damage. Although Amifostine, the widely used, FDA approved radio-protector, has been found to reduce the radiation induced pneumonitis during radiation therapy of non-small cell lung carcinoma, its application during mass and field exposure is limited due to associated toxicity and ineffectiveness with the oral administration. The amifostine analogue (DRDE-30) overcomes this limitation as it is orally effective in reducing the mortality of whole body irradiated mice. The current study was undertaken to investigate the potential of DRDE-30 to ameliorate radiation induced lung damage. DRDE-30 was administered intra-peritoneally, 30 minutes prior to 13.5 Gy thoracic (60Co-gamma) radiation in C57BL/6 mice. Broncheo- alveolar lavage fluid (BALF) and lung tissues were harvested at 12 and 24 weeks post irradiation for studying inflammatory and fibrotic markers. Lactate dehydrogenase (LDH) leakage, leukocyte count and protein content in BALF were used as parameters to evaluate lung vascular permeability. Inflammatory cell signaling (p38 phosphorylation) and anti-oxidant status (MnSOD and Catalase level) was assessed by Western blot, while X-ray CT scan, H & E staining and trichrome staining were done to study the lung architecture and collagen deposition. Irradiation of the lung increased the total protein content, LDH leakage and total leukocyte count in the BALF, reflecting endothelial barrier dysfunction. These disruptive effects were significantly abolished by DRDE-30, which appear to be linked to the DRDE-30 mediated abrogation of activation of the redox-sensitive pro- inflammatory signaling cascade, the MAPK pathway. Concurrent administration of DRDE-30 with radiation inhibited radiation-induced oxidative stress by strengthening the anti-oxidant defense system and abrogated p38 mitogen-activated protein kinase activation, which was associated with reduced vascular leak and macrophage recruitment to the lungs. Histopathological examination (by H & E staining) of the lung showed radiation-induced inflammation of the lungs, characterized by cellular infiltration, interstitial oedema, alveolar wall thickening, perivascular fibrosis and obstruction of alveolar spaces, which were all reduced by pre-administration of DRDE-30. Structural analysis with X-ray CT indicated lung architecture (linked to the degree of opacity) comparable to un-irradiated mice that correlated well with the lung morphology and reduced collagen deposition. Reduction in the radiation-induced inflammation and fibrosis brought about by DRDE-30 resulted in a profound increase in animal survival (72 % in the combination vs 24% with radiation) observed at the end of 24 weeks following irradiation. These findings establish the potential of the Amifostine analogue, DRDE-30, in reducing radiation induced pulmonary injury by attenuating the inflammatory and fibrotic responses.

Keywords : amifostine, fibrosis, inflammation, lung injury radiation
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